IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Application of:	**Clark T. Hung, et al.**	:	Group Art Unit:	1744
Serial No.:	10/049,761	:	Examiner:	W.H. Beisner
Filed:	February 7, 2002	:	Confirmation No.:	7596

For: **BIOREACTOR FOR GENERATING FUNCTIONAL CARTILAGINOUS TISSUE**

DECLARATION OF CLARK T. HUNG

Clark T. Hung hereby declares and says:

1. I am an Associate Professor in the Department of Biomechanical Engineering at Columbia University. I have held a faculty position in biomedical engineering since 1997.

2. I received an Sc.B. in Bioengineering from Brown University in 1990. I received an M.S.E. and a Ph.D. in Bioengineering from the University of Pennsylvania in 1992 and 1995, respectively. My doctoral dissertation was entitled "Real-Time Calcium Response to Fluid Flow in Cultured Bone Cells."

3. I have extensive experience in the art of biomedical engineering, especially with regard to the design and preparation of implants to replace or augment cartilaginous tissue in the human body. A copy of my curriculum vitae is attached hereto.

4. I am a co-inventor of the above-identified application.

5. I am familiar with the Office Action dated September 9, 2005, as well as the references cited therein, particularly Lee et al. (PCT published application No. WO 98/401111) (hereinafter referred to as "Lee") and Lee et al. (Journal of Orthopaedic Research) (hereinafter referred to as "Lee and Bader").

6. As explained further herein, the final tissue produced by Lee and Lee and Bader after 48 hours of applied loading is not functional cartilaginous tissue, i.e., tissue as defined in paragraph 29 of my published application as "possessing the mechanical, electrical, chemical, and biochemical properties of cartilaginous tissues -- the properties that permit cartilage to perform and maintain its load-bearing capacity."

7. Based on my experience, one of ordinary skill in the art of biomedical engineering considers the properties described in paragraphs 8, 9, and 10 to determine whether cartilaginous tissue produced in a bioreactor is functional cartilaginous tissue.

8. The mechanical properties of cartilaginous tissue include a compressive Young's modulus, which is a measure of stiffness. For native tissue, the compressive Young's modulus ranges from about 200 to about 1400 kPa, as described in paragraph 5 of my published application. These properties also include a hydraulic permeability, which is a measure of resistance to fluid flow through the tissue. For native tissue, the hydraulic permeability ranges from about 10^{-15} to about 10^{-16} m^4/Ns, as described in paragraph 6 of my published application.

9. The electrical properties of cartilaginous tissue include a streaming potential, which is the measured voltage generated by the flow of a charged ionic solution (e.g., a bathing solution in culture or a native interstitial fluid) through the GAG-rich (i.e., glycosaminoglycan-rich) matrix of cartilage during applied deformational loading.

10. The chemical and biochemical properties of cartilaginous tissue include a GAG content, which is a measure of proteoglycan content. For native tissue, the GAG content ranges from about 2.5 to about 10 % tissue wet weight (ww). These properties also include a collagen content. For native tissue, the collagen content ranges from about 5 to about 30 % ww.

11. Based on my experience, one of ordinary skill in the art of biomedical engineering customarily determines whether cartilaginous tissue produced in a bioreactor is functional cartilaginous tissue by quantitatively comparing the properties exhibited by that tissue with the properties exhibited by native tissue.

12. For example, based on my experience, one of ordinary skill in the art customarily considers tissue having a GAG content approaching about 1 % ww to be functional cartilaginous tissue. This threshold of functional GAG content is about an order of magnitude smaller than the upper range of the GAG content of native tissue.

13. A customary method for measuring the sulfated GAG content of cartilaginous tissue is to perform a so-called colorimetric assay. In such an assay, a sample of cartilaginous tissue is wet weighed, digested with an enzyme, exposed to a

standard colored dye (e.g., dimethylmethylene blue), and then observed with a spectrophotometer. GAG molecules in the sample bind to the dye and cause a color change in the sample that can be measured with the spectrophotometer. The GAG content of the sample can be determined from a calibration curve of spectrometer measurement readings and known standard concentrations of GAG.

14. Lee produces a tissue product after 48 hours of applied loading. (See, e.g., Lee examples 6 and 10.) Lee does not provide any quantifiable evidence from which one of skill in the art could conclude the final tissue product to be functional based on its mechanical, electrical, chemical, and/or biochemical properties.

15. More specifically, Lee does not provide any quantifiable evidence at all related to the mechanical, electrical, chemical, and biochemical properties of the final tissue product after 48 hours of applied loading. At most, Lee provides graphs of cell metabolic activity in Figs. 8a and 8b that merely show increased sulfate incorporation (a measure of GAG synthesis rate) and thymidine incorporation (a measure of DNA synthesis rate), respectively, in dynamically loaded constructs compared to the unloaded (control) scaffold. Since these radiolabel incorporation assays represent only the metabolic state of the cells, the graphs do not provide any basis for a quantitative determination of the GAG content (i.e., actual GAG that has been deposited by the cells into the construct) of the final tissue product after 48 hours of applied loading.

16. Based on my experience and the foregoing observations, one of ordinary skill in the art would not consider the final tissue product of Lee to be functional cartilaginous tissue.

17. Lee and Bader also produce a tissue product after 48 hours of applied loading. (See, e.g., Lee and Bader "Results.") Like Lee, Lee and Bader do not provide any quantifiable evidence from which one of skill in the art could conclude the final tissue product to be functional based on its mechanical, electrical, chemical, and/or biochemical properties.

18. More specifically, Lee and Bader do not provide any quantifiable evidence related to the mechanical and electrical properties of the final tissue product after 48 hours of applied loading.

19. Lee and Bader do, however, provide quantifiable evidence of chemical and biochemical properties of the final tissue product after 48 hours of applied loading. As described in the Lee and Bader "Results" section, the final tissue product has a GAG content of 42.8×10^{-6} g GAG/10^6 cells. Lee and Bader specify the relationship between cell density and construct wet weight to be 1×10^6 cells = 0.255 g. (See Lee and Bader, p. 183, col. 2, ll. 2-5). Using this conversion factor, the Lee and Bader final tissue product has a GAG content of (42.8×10^{-6} g GAG/10^6 cells) x (1×10^6 cells/0.255 g) = 0.017 % ww. Lee and Bader do not provide any quantifiable evidence of other chemical and/or biochemical properties of the final tissue product.

20. As noted in paragraph 12, the threshold GAG content of functional cartilaginous tissue is about 1 % ww. The GAG content of the Lee and Bader final tissue product (i.e., 0.017 % ww) is, therefore, about two orders of magnitude smaller than the threshold GAG content of functional cartilaginous tissue.

21. Based on my experience and the foregoing observations, one of ordinary skill in the art would not consider the final tissue product of Lee and Bader to be functional cartilaginous tissue.

22. In summary, neither Lee nor Lee and Bader teaches or suggests the production of functional cartilaginous tissue.

Date: March 9, 2006

Clark T. Hung

CLARK T. HUNG, PH.D.

2/14/06

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FIELD OF SPECIALIZATION

Physical effects on cells and orthopaedic cell mechanotransduction and tissue engineering.

ACADEMIC TRAINING

University of Pennsylvania — *Philadelphia, PA*
PH.D., BIOENGINEERING, 12/95.
Dissertation: *Real-Time Calcium Response to Fluid Flow in Cultured Bone Cells.*
Advisor: Drs. Solomon R. Pollack and Carl T. Brighton

University of Pennsylvania — *Philadelphia, PA*
M.S.E., BIOENGINEERING, 5/92.
Advisor: Dr. John L. Williams

Brown University — *Providence, RI*
SC.B., BIOENGINEERING, 5/90.

HONORS/AWARDS

1990-95 NIH Bone & Cartilage Traineeship (Department of Orthopaedic Surgery, University of Pennsylvania, Philadelphia, PA)

1996 Postdoctoral Fellowship (NASA- Wistar Institute-Bioengineering, University of Pennsylvania, Philadelphia, PA)

1996 Solomon R. Pollack Award for Excellence in Graduate Bioengineering Research (Department of Bioengineering, University of Pennsylvania, Philadelphia, PA)

1997 Whitaker Special Opportunity Award Postdoctoral Fellowship (Center for Biomedical Engineering, Columbia University, New York, NY)

2000 Guest editor with Drs. Farshid Guilak and Ray Vanderby for special Cell & Tissue Engineering issue of *J Biomech Eng* (June 2000).

2002 Edward and Carole Kim Award for Faculty Involvement (Fu Foundation School of Engineering & Applied Science, Columbia University, New York, NY)

2003 NEGMA-LERADS Prize; 3rd International Symposium on Mechanobiology of Cartilage and Chondrocyte, Brussels, Belgium, May 16-17, 2003.

2004 Co-author, The John Paul Stapp Best Paper Award in the 2003 Stapp Car Crash Journal presented at the 47th Stapp Car Crash Conference. *A tissue level tolerance criterion for living brain developed with an in vitro model of traumatic mechanical loading* (Morrison III, B lead author)

2005 Invited White Paper Author and Moderator: Biomechanics Curriculum Workshop at the Whitaker Foundation Educational Summit II, Landsdowne, VA, March 3-6, 2005.

PROFESSIONAL SOCIETIES/ACTIVITIES

American Society for Mechanical Engineers (ASME): Bioengineering Division- Cell and Tissue Engineering Committee, Biomedical Engineering Society (BMES), Orthopaedic Research Society (ORS)

Ad-hoc Reviewer: *Clin Orthop Rel Res, Biophys J, J Biomechanics, J Orthop Res, J Biomech Eng, Arthritis Research, Arthritis Rheumatism, Biochem Biophysica Acta, J Microscopy, Bone, J Bone Miner Res, Osteoarthritis Cartilage, Calcified Tissue, Ann Biomed Eng, Tissue Eng, Acta Biomaterialia, Med Eng Physics*

1999 Session Organizer and Chair, ASME Summer Bioengineering Conference 1999 (Redmond, MT): 6 *Tissue Engineering* sessions with Drs. Farshid Guilak and Ray Vanderby

1999 Session Organizer and Chair,1999 ASME Winter Meeting (Nashville, TN) 2 sessions on Cell Mechanics

2000 Session Organizer and Chair, 2000 ASME Winter Meeting (Orlando, FL): a) *Cell Mechanics*; b) *Tissue Engineering*

2001 Session Moderator, *Cartilage Mechanics*, 47th Annual Meeting of the Orthopaedic Research Society (San Francisco, CA).

2001 Session Organizer and Chair, 2001 ASME Summer Bioengineering Conference (Snowbird, Utah): a) *Orthopaedic Tissue Engineering*; b) *Cellular Engineering*

2001 Session Organizer and Chair for 2001 BMES Annual Meeting (Durham, NC): *Mechanotransduction III*

2001 Session Chair, 2001 ASME Winter Meeting (New York, NY): *Tissue Engineering*

2001 Ad hoc Reviewer for Singapore Biomedical Research Council Grants (September)

2002 Session Moderator: *Cartilage Mechanics*, 48th Annual Meeting of the Orthopaedic Research Society (Dallas, TX).

2002 Session Organizer, 2002 ASME Winter Meeting (New Orleans, LA): a) *Cellular Engineering & Mechanics*; b) *Tissue Engineering*

2003 Session Organizer and Chair, 2003 ASME Summer Bioengineering Conference (Key Biscayne, FL): *Orthopaedic Cell & Tissue Engineering*- 2 sessions.

2003 Phone Reviewer for National Institute of Dental and Craniofacial Research (NIDCR) R03 grant applications, July 19.

2003 Reviewer for CSR special emphasis panel ZRG1 SSS-U(40) for biomedical technology resource grant (NIH P41) at Tufts University (July 21-23).

2003 Reviewer for abstract submissions to 50th Annual meeting of the Orthopaedic Research Society

2004 Phone Reviewer for National Institute of Dental and Craniofacial Research (NIDCR) R03 grant applications, February 19.

2004 Reviewer for CSR special emphasis panel ZRG1 BST-D (40) for biomedical technology resource grant (NIH P41) (Old Town, VA, April 7-8).

2004 Mail Reviewer: for South Carolina NASA/EPSCoR Research Grant Program

2004 Mail Reviewer: for CSR Skeletal Biology Development and Disease (SBDD) study section R21 grant applications, June 27.

2004 Co-Chair/Organizer: 3 sessions on Orthopaedic Mechanobiology at 2004 BMES Annual Meeting (Philadelphia, PA)

2004 Reviewer for abstract submissions to 51st Annual meeting of the Orthopaedic Research Society

2004 Mail Reviewer: Aircast Foundation

2004 Mail Reviewer: Swiss National Science Foundation, Division of Biology and Medicine

2005 Session Moderator: *Molecular and Cellular Mechanics*, 51st Annual meeting of the Orthopaedic Research Society (Washington, D.C.)

2005 Phone Reviewer: NIBIB (Marc Rigas, NIH/CSR); March 28, 2005.

2005 Session Chair: 2005 Summer Bioengineering Conference, Vail, CO: *Cell and Molecular Engineering I & II, Cartilage Tissue Engineering*

2005 Phone Reviewer: Reviewer for CSR Telephone special emphasis panel (ZRG1 MOSS-K 04), July 15

2005 Reviewer for abstract submissions to 52nd Annual meeting of the Orthopaedic Research Society

2005- Vice Chairman, Cell and Tissue Engineering Committee, Bioengineering Division of the American Society for Mechanical Engineers

2006- Associate Editor, *Journal of Biomechanical Engineering* (term to begin Januray 1)

PATENTS

A full US patent application entitled: *Bioreactor for Generating Functional Cartilaginous Tissue* by Hung et al. has been submitted February 7, 2002.

INVITED LECTURES

1. Seminar Speaker: *Real-Time Calcium Response to Fluid Flow in Cultured Bone Cells*; The Hospital for Special Surgery, New York, NY, August 12, 1995
2. Seminar Speaker: *Real-Time Calcium Response to Fluid Flow in Cultured Bone Cells*; Columbia University, Department of Mechanical Engineering, New York, NY, December 2, 1995
3. Seminar Speaker: *Real-Time Calcium Response to Fluid Flow in Cultured Bone Cells*; Tulane University, Department of Biomedical Engineering, New Orleans, LA, September 10, 1996
4. Seminar Speaker: *Anterior Cruciate and Medial Collateral Ligament Fibroblasts Exhibit Different Calcium Responses to Fluid Flow;* Columbia University, Center for Biomedical Engineering, New York, NY, January 23, 1997
5. Seminar Speaker: *Chondrocyte Response to Fluid-induced Shear Stress*; Advanced Tissue Sciences, LaJolla, CA, June 1997
6. Seminar Speaker: *Real-Time Calcium Response to Fluid Flow in Cultured Bone Cells*; Indiana Bone & Mineral Group, Indianapolis, IN, February 24,1999
7. Guest lecturer in BME 1001 Engineering in Medicine, *Cartilage Tissue Engineering*; Department of Biomedical Engineering, New York, NY, February 28, 2000.
8. Seminar Speaker: *Chondrocyte Response to Osmotic Loading: Experimental and Theoretical Studies;* University of Massachusetts Medical Center, Worcester, MA, January 29, 2001
9. Invited Speaker: *Functional Tissue Engineering of Articular Cartilage;* University of Nancy, France, April 23, 2001.
10. Plenary Speaker: *Functional Tissue Engineering of Articular Cartilage;* EuroMech Colloquium 420: Mechanobiology of Cells and Tissues, Nancy, France, April 25,2001
11. Invited Speaker: *Determination of the Chondrocyte Environment within Cartilage Subjected to Loading: Theoretical and Experimental Approach*; 2nd International Symposium on Mechanobiology of Chondrocytes and Cartilage, Paris, France, April 27, 2001.
12. Invited Speaker: *Cell & Tissue Culture Techniques: A Tutorial*; 2001 ASME Summer Bioengineering Conference, Snowbird, UT, June 29, 2001.
13. Invited Speaker: *Functional Tissue Engineering of Articular Cartilage*; Columbia Class of 1951 Reunion, Arden House, Harriman, NY, September 8, 2001.
14. Invited Speaker: *Fluid Flow Effects on Bone Cells: Influence of Flow-Cell-Substrate Interactions and Cell Mechanical Properties*; Fluid Flow in Bone Workshop, Phoenix, AZ, October 11, 2001.
15. Invited Speaker: *Fluid Flow Effects on Bone Cells: Influence of Flow-Cell-Substrate Interactions and Cell Mechanical Properties*; NYC Mineralized Tissue Seminar, New York, NY, December 12, 2001.
16. Invited Speaker: *Tutorial: Biomechanical Factors in Tissue Engineering: Bioreactors*; 48th Annual Meeting of the Orthopaedic Research Society Meeting, Dallas, TX, February 10, 2002.

17. Invited Speaker: *A Paradigm for Functional Tissue Engineering of Articular Cartilage*, Stanford University Bio X Sponsored Symposium on Cartilage Tissue Engineering, Palo Alto, CA, March 22, 2002.
18. Invited Speaker: *Biomechanical Factors in Tissue Engineering: Bioreactors;* Biomedical Technology Track sponsored Bioreactor Design Tutorial at the 2002 Winter Annual ASME Meeting, New Orleans, LA, November 20, 2002.
19. Invited Speaker: *A Paradigm for Functional Tissue Engineering of Articular Cartilage*, Department of Mechanical Engineering, Georgia Institute of Technology, Atlanta, GA, April 22, 2003.
20. Invited Speaker: NEGMA-LERADS prize lecture: *A Paradigm for Functional Tissue Engineering of Articular Cartilage*, 3rd International Symposium on Mechanobiology of Cartilage and Chondrocyte, Brussels, Belgium, May 16-17, 2003.
21. Invited Speaker: *A Paradigm for Functional Tissue Engineering of Articular Cartilage using Applied Deformational Loading*, 4th International Conference on Tissue and Genetic Engineering, Boston, MA, April 1-2, 2004.
22. Invited Lecture: *Engineering Biological Replacements for Joints*, Columbia University Southern California Dean's Day Symposium, West Hollywood, CA, March 13, 2004.
23. Invited Lecture*: A Functional Tissue Engineering Strategy for Repair and Replacement of Osteoarthritic Cartilage*, European Society of Biomechanics 2004, the Netherlands, July 4-7, 2004.
24. Invited Lecture*: Chondrocyte Mechanotransduction: Cartilage Basic Science to Tissue Engineering*, Department of Biomedical Engineering, Purdue University, West Lafayette, IN, September 24, 2004.
25. Invited Lecture*: Chondrocyte Mechanotransduction: Cartilage Basic Science to Tissue Engineering*, Brown University, May 5-6, 2005.
26. Invited Speaker: *Chondrocyte Mechanotransduction: Cartilage Basic Science to Tissue Engineering, Society* of In Vitro Biology Conference, June 4-7, 2005, Baltimore, MD
27. Invited Speaker: *Cartilage Biomechanics and Tissue Engineering*, Stryker Medical, Mahwah, NJ, July 22, 2005.
28. Invited Speaker: *Cartilage Tissue Engineering: Implications of Applied Deformational Loading and Solute Transport*. McGowan Institute for Regenerative Medicine, University of Pittsburgh, October 6, 2005.
29. Invited Speaker: *Cartilage Tissue Engineering: Implications of Applied Deformational Loading and Solute Transport*. Department of Orthopaedic Surgery Grand Rounds and Department of Biomedical Engineering Seminar Series, University of California-Irvine, December 1, 2005.

TEACHING RECORD

1. BMEN 4001,3001 Biomedical Engineering Principles I – (Fall '99,'00) quantitative molecular/cell biology- enrollment 40 students
2. BMEN 4002,3002 Biomedical Engineering Principles II – (Spring '98,'99) quantitative physiology- enrollment 40 students
3. BMEN 4501 Tissue Engineering I (Fall '98, '99,'00, '01, '02,'03, '04)- current enrollment 74 students and taught as an offering of the Columbia Video Network (CVN).
4. BMEN 3820 Biomedical Engineering Laboratory II (Spring '01,'02,'03,'04)- current enrollment 58 students
5. BMEN 3830 Biomedical Engineering Laboratory III (Fall '99)- enrollment 40 students
6. BMEN 4502 Tissue Engineering II (Spring '00) - enrollment 50 students
7. BMEN 3840 Biomedical Engineering Laboratory (Spring '99)- enrollment 40 students
8. BMEN 3998 Independent Research Advisor: (Spring '00- present) – 3 students/semester

9. BMEN 3910 Senior Design (Spring '99- present): 5 students- Advisor for projects aimed at chamber for osmolarity studies ('98), a methodology to make alginate slabs ('99); device to measure direct hydraulic permeability of soft hydrated tissues ('00), alginate hollow microspheres ('01,'02,'03). For Spring '04: *in vitro* cartilage repair (4 students) model, pressure/deformation bioreactor design (4 students) and sperm motility projects (4 students)
10. G3200 Cellular Sensing, Transduction, and Amplification of Mechanical Forces (Spring '05; City College of New York biomedical engineering course directed by Professor Sheldon Weinbaum): instructor for module on cartilage mechanotransduction (10 students).
11. Summer BME High School Course: *Physical Effects on Cells* (July 99- present)- 20-24 high school students per year. Course developed and administered through the Columbia High School Programs, Columbia Continuing Education and Special Programs. The month long course provides an introduction to the multidisciplinary field of biomedical engineering and the application of engineering principles to solving problems in biology, physiology, and medicine. International students have also participated in this course. Teaching assistants are BME undergraduate or graduate students.

FELLOWS/STUDENTS/ STAFF SUPERVISED

Postdoctoral Fellows: present position
1. Glyn D. Palmer, Ph.D. (9/99-12/00): Postdoctoral fellow at Center for Molecular Orthopaedics, Harvard Medical School, Boston, MA
2. Michelle A. LeRoux-Williams, Ph.D. (9/00-10/01): Development engineer at Osiris Therapeutics, Baltimore, MD
3. Christopher C-B. Wang, Ph.D. (8/01-6/03): Research analyst, American Express, New York, NY

Doctoral Students: dissertation title
1. Co-Advisor: Christopher C-B. Wang (7/99- 8/01): Ph.D. thesis in Mechanical Engineering: *Functional properties of cartilage and environment of chondrocytes: experiments and theoretical analyses*
2. Co-Advisor: Robert L. Mauck (8/98-7/29/03): Ph.D. thesis in Biomedical Engineering: *Functional tissue engineering of articular cartilage: The effect of physical forces on the in vitro growth of engineered constructs*
3. Advisor: Pen-Hsiu Grace Chao (1/99-8/05): Ph.D. thesis in Biomedical Engineering: *Physical forces on cells: effects of applied osmotic loading and direct current electric fields*
4. Advisor: Terri-Ann N. Kelly (1/00-)- BME doctoral candidate
5. Co-Advisor: Nadeen O. Chahine (9/00-): BME doctoral candidate
6. Co-Advisor: Eric G. Lima (9/01-): BME doctoral candidate
7. Advisor: Kenneth W. Ng (9/01-): BME doctoral candidate
8. Advisor: Mandy Ho (9/02-): BME doctoral candidate
9. Advisor: Elizabeth S. Oswald (9/04-): BME doctoral candidate
10. Advisor: Liming Bian (1/05-): BME doctoral candidate

Master's Students: present position
1. Louis Cappezuto, J.D. (1/02-5/02): M.S., Biotechnology Program (consul at Johnson and Johnson)
2. Amir Hakakha, M.S.E. (1/01-9/01): Ortec, Manager of Technology Development, New York, NY
3. HyukJin Lee, M.S.E. (8/03-5/04): Recently Graduated
4. Shelley Han, M.S.E., (1/02-7/04): Industry
5. Patricia B. Setti, M.S.E., (9/04-12/04): Stryker Orthopaedics (Regulatory Affairs), Mahwah, NJ

Undergraduate Students: present position
1. Rani Roy, FFSEAS '00: Ph.D. candidate at Cornell University BME

2. Sarah Desoky, FFSEAS '00: NA
3. Lia Hondroulis, FFSEAS '00: Andrx Pharmaceuticals (candidate for law school)
4. Wendy Liu (MIT '00, summer 1999): Ph.D. candidate at Johns Hopkins BME
5. Dennis Wong, FF SEAS '01: Working at the National Security Agency
6. Brian Kim, FF SEAS '01: Premed coursework at Columbia
7. Aparna Prasad, FF SEAS '01: Medical student at SUNY Buffalo Medical School
8. Nelly Andarawis, FF SEAS '01: Ph.D. candidate at University of Pennsylvania BME
9. Kelly Jamieson, FF SEAS '02: Research Technician at Mt. Sinai Medical Center
10. Laura Rummler, FF SEAS '02: Research engineer at Peripheral Nerve Research Laboratory, UC Irvine; Doctoral candidate UC Irvine
11. Nicole Gabriel (Rice University '03, summer 2002): Ph.D. candidate at University of Pennsylvania BME
12. Elizabeth Oswald, FF SEAS '04: Will be attending Columbia University BME as a doctoral candidate in the fall.
13. QiQi Cheng, FF SEAS '04: Ph.D. candidate at University of Pennsylvania BME
14. Christopher DuBois, FF SEAS '04: Ph.D. candidate at University of Pennsylvania BME
15. Selom Gasinu, FF SEAS '04: Attending Temple Medical School
16. Michael Bazylewicz, FF SEAS '04 (summer 2004): Attending Darthmouth College Medical School
17. Mathew Fisher, FFSEAS'05: Will be attending University of Pittsburgh BME as a doctoral candidate
18. Lauren Statman, FFSEAS '05: Will be attending UCSF Bioengineering as a doctoral candidate
19. Anne-Marie Cannon (Rice University '05, summer 2003): employed at Xenogen Biosciences, in Cranbury NJ
20. Fran Navratil, FFSEAS '04: MTV, New York, NY
21. Jesse Martin, FFSEAS'05
22. Timon Tai, FFSEAS '06
23. Gilad Landan FFSEAS '06
24. Whitney Booker, FFSEAS '05

Medical Students: present position
1. Frank Raia, M.D.: Orthopaedic resident at Columbia-Presbyterian
2. Ross Henshaw, M.D.: Orthopaedic resident at Columbia-Presbyterian
3. Sansan S. Lo, M.D.: (9/00-5/01): Orthopaedic resident at Columbia-Presbyterian

Orthopaedic Residents
1. Justin Saliman, M.D.: (1/04-3/04) Orthopaedic resident at St. Luke's-Roosevelt
2. David Capiola, M.D.: (3/04-5/04) Orthopaedic resident at St. Luke's-Roosevelt
3. Steve Quinnan, M.D.: (1/05-3/05 Orthopaedic resident at St. Luke's-Roosevelt
4. Darren Friedman, M.D.: (3/05-5/05) Orthopaedic resident at St. Luke's-Roosevelt

Lab Manager: present position
1. Sara Seyhan, B.S.E.: (2/00-2/02) Associate Engineer at Anterogen Co., Ltd.

DISSERTATION COMMITTEES

1. Michael Huang (MSE,'98): *Development of an apparatus and technique to measure calcium binding in skeletal and cardiac muscle* (examiner)
2. Andrey Levchenko (DES, '98): *Expression and action of P-glycoprotein: A quantitative analysis*
3. Hong An (Ph.D., '99; Chem Eng): *Cell deformation in an asymmetric thin liquid film* (examiner)
4. Shawn Gomez (EngScD ,'99*): Attachment of cells to surfaces under controlled fluid flows* (examiner)

5. Sarah Patrick (Ph.D., '99): *Control of receptor-ligand contact to examine the kinetics of T cell activation* (examiner)
6. Michael Soltz (Ph.D., '00; Mech Eng): *Investigation of a boundary friction model for articular cartilage: Effects of interstitial fluid pressurization and surface topography* (examiner)
7. Chun-Yuh Huang (Ph.D., '01): *Biomechanics of soft tissues in the shoulder joint-glenohumeral cartilage, ligament, and rotator cuff tendon* (examiner)
8. Sobin Kim (Ph.D., '01; Chem Eng): *Kinetics of calcium mobilization of a T cell activated by controlled receptor-ligand contact* (examiner)
9. Vincent Wang (Ph.D., '01; Mech Eng): *Biomechanics of the normal and surgically reconstructed shoulder* (examiner)
10. *Stavroula* Sofou (Ph.D., '01; Chem Eng): *Control of phospholipid vesicle organization with cysteine-containing oligopeptides* (examiner)
11. Changbin Wang (Ph.D., '01; Mech Eng): *Digital video microscopy-based determination of cartilage inhomogeneity, anisotropy and tension-compression nonlinearity: Implications on chondrocyte environment* (co-sponsor)
12. Chi Hyun Kim (EngScD,'03; Mech Eng): *In vivo trabecular bone response to mechanical loading and parathyroid hormone stimulation* (chairman, examiner)
13. Zhongliang Tang (Ph.D., '03; Chem Eng): *Microfluidics: fluid flow, transport, control, characterization and applications* (examiner)
14. Robert Mauck (Ph.D., '03): *Functional tissue engineering of articular cartilage: The effect of physical forces on the in vitro growth of engineered constructs* (co-sponsor)
15. Vedran Knezevic: Doctoral proposal: *A system for biaxial loading of fibroblast-populated collagen gels for the study of mechanobiology* (examiner)
16. Pen-Hsiu Grace Chao (Ph.D., '05): Doctoral proposal: *Physical forces on cells: effects of applied osmotic loading and direct current electric fields* (sponsor)
17. Mia Mia Thi (City College of New York): Doctoral proposal: *Effects of fluid shear stress on bone cell gap junctional communication* (examiner)
18. Patrick Johnson (Ph.D., '04; Chem Eng): *Polymer-anchored DNA monolayers for electrochemical sensing* (examiner)
19. Peng Wang (Ph.D., '04; Chem Eng): *Polymeric thin films: preparations, surface modification and morphology* (examiner)
20. Erica Takai (Ph.D., '05): *Modulation of Bone Cell Mechanotransduction* (examiner)
21. Seonghun Park (Ph.D., '05, Mech Eng)): Doctoral pre-proposal and proposal: *Interstitial fluid flow-dependent and flow-independent mechanical and tribological response of articular cartilage* (Mech Eng) (examiner)
22. Nadeen Chahine: *Cartilage Biomechanics* (Biomed Eng) (co-sponsor)
23. Terri-Ann Kelly: Doctoral pre-proposal (Biomed Eng): *Characterization and optimization of chondrocyte-seeded agarose constructs grown in free-swelling and dynamic- loading culture* (sponsor)

EMPLOYMENT RECORD

1995 Instructor, Department of Bioengineering, University of Pennsylvania, Philadelphia, PA (Fall)

1996 Postdoctoral Fellow, Department of Bioengineering, University of Pennsylvania, Philadelphia, PA (NASA microgravity-bioreactor studies- 1/96-6/96); Postdoctoral Fellow, Orthopaedic Research Laboratory, Center for Biomedical Engineering, Columbia University, New York, NY (cartilage research- 7/96-6/97)

1997-2002 Assistant Professor of Biomedical Engineering, Fu Foundation School of Engineering & Applied Science (FFSEAS); Associate, Orthopaedic Research; Columbia University, New York, NY (appointed 7/97)

1998- Director, Cellular Engineering Laboratory, FFSEAS

1999- Director, July summer high school course *Physical Effects on Cells: Biomedical Engineering*, Columbia University, New York, NY

1999-2003 Department of Biomedical Engineering undergraduate and graduate committee member, sophomore class advisor, Biomedical Engineering Society (BMES) faculty advisor

2000- Cellular Engineering Faculty Search Committee Member, Department of Biomedical Engineering, FFSEAS

2000- Faculty advisor for Biomedical Engineering graduate students association (GraBME).

2002- Associate Professor of Biomedical Engineering, FFSEAS

2004- Associate Professor of Biomedical Engineering with tenure, FFSEAS (May)

2004- Member, Nominating Committee, FFSEAS

2003-2005 Chair, Undergraduate Committee, Department of Biomedical Engineering, FFSEAS

JOURNAL ARTICLES

1. Hung CT, Williams JL: A method for inducing equi-biaxial and uniform strains in elastomeric membranes used as cell substrates. *J Biomechanics* 27(2):227-232, 1994.
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ACTIVE GRANTS

1. **Principal Investigator:** NIH: NIAMS 2R01AR46568-05A2: *Physiologic loading for cartilage tissue engineering*; approximate yearly direct cost:$200,000, 4/1/05-12/31/08 (total cost for entire granting period: $1,200,000)- 25% yearly effort. Description: This COMPETING RENEWAL continues our investigation of the use of applied physiologic loading in a custom bioreactor to grow functional articular cartilage. Bovine/canine chondrocytes are encapsulated in agarose hydrogels and subjected to physiologic loading in long-term cultures. Tissue material properties and biochemical composition are measured and compared to those of native cartilage. The aims of the grant are extended to study the effects of combined deformational loading with direct media perfusion, as well as the effects of loading boundary conditions on the development of tissue inhomogeneity and surface properties.

2. **Principal Investigator:** NIH: NIAMS 1R01 AR49922-04: *Intervertebral disc response to cyclic loading in vivo*, $164,500 yearly direct cost ($1,041,497 total cost), 9/26/02-8/31/06, 20% yearly effort. Description: The aim of this grant is to investigate the material and biochemical properties (e.g., aggrecan, collagen and cartilage oligomeric matrix protein) of the intervertebral disc subjected to well-controlled loading regimens in an in vivo rat-tail model.

3. **Co-Investigator:** NIH: NIAMS 1R01AR46532-05 (Ateshian PI): *Anisotropy and nonlinearity of cartilage mechanics*; approximate yearly direct cost:$200,000, 2/1/04-1/31/09 (total cost for entire granting period: $1,571,996)- 20% yearly effort. Description: This COMPETING RENEWAL continues to to develop a model for articular cartilage that can explain its anisotropic and nonlinear behavior (in tension and compression). It proposes a hierarchial series of progressively more complex experiments from the joint to the cellular level. Dr. Hung plays a role primarily in the measurement of cartilage material properties and tissue inhomogeneity, and local strain environment around the cell using custom loading devices mounted on an epifluorescence microscopy system.

4. **Co-Investigator:** NIH: NIAMS R01 AR43628-09 (Ateshian, PI): *Biotribology of diarthrodial joints*; (total cost: $1,766,739)- 6/1/04-5/31/09- 10% yearly effort. This grant represents a competing renewal that will use AFM, TIRF and custom testing devices to assess the role of the superficial zone and potential lubricants (such as lubricin or SZP protein) on diarthrodial joint lubrication.

5. **Co-Principal Investigator:** National Science Foundation (NSF) MCB-0423475 (J. Chloe Bulinski, PI): *Probing mechanisms of cell motility in electric fields* (total cost: $350,001)- 8/1/04-7/31/06- one month summer support. Description: This grant will investigate mechanisms (e.g., cell surface charge, enzymatic treatments, polycation and polyanions, cytoskeleton) on 3T3 Fibroblast orientation and directed migration to DC electric fields, in sparse and wounded monolayer cultures. Bioengineering analysis and microfluidic systems will be applied.

6. **Co-Investigator:** NIH R21 AR052417-01A1 (Edward Guo, PI): *Microfluidics and Bone Mechanotransduction*; granting period: $275,000 total direct costs- 10% effort, 1/01/06-12/31/07. Description: Use microfluidic technology to study osteocyte and osteoblast mechanotransduction to mechanical stimuli in a 2D and 3D model system. The role of cell-cell communication will be examined with respect to gap junction role in mediating intracellular calcium transients measured using fluorescence microscopy.

7. **Consortium Principal Investigator:** NIH 1R21AR053530-01 subcontract from University of Missouri (James L. Cook, PI): *Tissue engineered osteochondral patella resurfacing*; total costs: $420,323 (total subcontract amount $165,000)- 2.5% effort, 3/1/06-2/28/08. Description: This application seeks to fabricate a tissue engineered osteochondral patella construct for implantation in a canine in vivo model. The Columbia subcontract will take canine cells from the Comparative Orthopaedic Laboratory and culture osteochondral patella constructs that will subsequently be implanted into canine knees in Missouri.

GRANTS PENDING

1. **Principal Investigator:** NIH: NIAMS 1R01AR052871-01A1: *Chondrocyte mechanotransduction using microfluidics*; 25% yearly effort; approximate yearly direct costs: $225,000, 4/1/06-3/31/10 (total cost for entire granting period: $1,400,000). Description: This grant will study the dynamic osmotic loading response of cultured chondrocytes using a custom microfluidics device. The role of cell size change and osmotic load magnitude/frequency on the intracellular calcium signaling response and subsequent cytoskeletal rearrangement and aggrecan gene expression of chondrocytes will be assessed. (SCORE: **161; 9.1%)**

2. **Co-Investigator:** NIH (Gerard Ateshian, PI): *Solute transport in cartilage tissue engineering*; 20% academic and 33% summer effort, 12/01/05-11/30/09. Description: This grant will investigate the use of mixture theory to model deformational loading-induced solute transport in hydrogel constructs as a potential mediator of enhanced tissue construct growth observed with daily applied deformational loading. Theoretical analyses will be complemented with experimental methodologies including photobleaching studies for determination of solute diffusion coefficients, direct hydraulic permeability and Aggregate modulus measurements of constructs, and confocal microscopy of solute transport real-time in axially loaded cell-free and cell-seeded cylindrical constructs.

PAST GRANTS

1. **Principal Investigator:** (subcontract from University of Wisconsin) NIH: NIAMS R01 AR45753 (Wilmot Valhmu PI): *Flow-induced MAPK and calcium signaling in chondrocytes*); approximate yearly direct cost: $87,262, 4/1/00-8/30/02 (co-PI of original grant received 9/98), (total cost for entire granting period: $115,090)- 25% academic and 33% summer effort. Description: The aim of this grant is to elucidate the role of mitogen activated protein kinases and calcium in chondrocyte mechanotransduction to fluid-induced shear stress. A major component of the grant is to delineate between concomitant stimuli that exist in the flow studies (e.g., electrokinetic phenomena, transport, shear rate).

2. **Principal Investigator:** Whitaker Biomedical Research Grant: *Shape changes and directed migration in chondrocytes to DC electric field*s; approximate yearly direct cost:$70,000, 5/1/99-4/30/02 (total cost for entire period: $209,999)- 20% annual effort. Description: This grant examines the mechanism behind chondrocyte galvanotropism and galvanotaxis, shape change and directed migration in response to applied direct current electric fields. Studies include the examination of cell surface charge, cell-substrate interactions, and nature of the applied electric field stimulus.

3. **Principal Investigator:** (subcontract from Conversion Energy Enterprises, Spring Valley, NY; SBIR Phase I) NIH: NIAMS 1R43AR48738-01 (Soltz PI): *Laser-assisted cartilage repair using collagen adhesives;* $30,000 total cost, 5/15/02-10/15/02- 10% effort. Description: The aim of this grant is to investigate the efficacy of laser activated collagen formulations as an adhesive and as an acellular graft that permits and/or promotes cell invasion.

4. **Principal Investigator:** Whitaker Foundation*: Transitional Funding: Microfluidic device for osmotic loading of cultured chondrocytes* ($80,000 total cost), 5/1/02-4/30/03, 20% yearly effort. Description: The aim of this grant is to develop a microfluidic device capable of subjecting cultured chondrocytes to time-varying osmotic loading while permitting study of their biological response (e.g., cell shape and volume change, aggrecan gene expression).

5. **Principal Investigator:** NIH: NIAMS 1R01AR46568-04 *Supplement*: approximate yearly direct cost:$29,000, 1/1/00-12/31/03 (total cost for entire granting period: $157,519) Description: Minority supplement for Terri-Ann Kelly (GRA) to expand the aims of the parent grant to study the development of inhomogeneous material and biochemical composition of chondrocyte-seeded agarose disks subjected to physiologic loading, using a microscopy-based system to measure tissue strains using a digital image correlation technique.

6. **Co-Investigator:** NIH: NIAMS 1R01AR46532-04 (Gerard Ateshian PI): *Anisotropy and nonlinearity of cartilage mechanics*; approximate yearly direct cost:$124,711, 2/1/00-1/31/03 (total cost for entire granting period: $724,337)- 20% academic and 30% summer effort. Description: This aim of this grant is to develop a model for articular cartilage that can explain its anisotropic and nonlinear behavior (in tension and compression). Dr. Hung plays a role primarily in the measurement of cartilage material properties and tissue inhomogeneity using custom loading devices mounted on an epifluorescence microscopy system.

7. **Co-Investigator/Consultant:** The Aircast Foundation (Ranjan Gupta PI: *Schwann cell response to the biomechanical forces associated with carpal tunnel syndrome*, $50,000/year, 6/03-5/05- 5% effort year 1. Description: This grant, awarded to Dr. Ranjan Gupta at UC Irvine, investigates the Schwann cell response to a reproducible, quantifiable mechanical stimuli in a controlled, physiologic environment. These studies will utilize parallel plate flow chambers and use various strategies to delineate between concomitant flow related stimulus in regulation of pro-myelogenic markers (MBP, MAG) as well as iNOS and VEGF mRNA.

8. **Principal Investigator:** NIH administrative supplement for nano-scale research related to NIAMS 1R21 AR48791-03. *Supplement for incorporation of laser tweezers* ($50,000 total cost), 9/30/03-9/29/04. Supplement to establish research collaboration with Dr. Michael Sheetz, Department of Biological Sciences at Columbia University, to incorporate laser tweezers and magnetic bead pulling system to the project.

9. **Principal Investigator:** National Institutes of Health (NIH): National Institutes of Arthritis, Musculoskeletal and Skin Diseases (NIAMS) 1R01AR46568-05: *Physiologic loading for cartilage tissue engineering*; approximate yearly direct cost:$143,890, 1/1/00-12/31/04 (total cost for entire granting period: $831,444)- 20% academic and 33% summer effort. Description: This grant investigates the

use of applied physiologic loading in a custom bioreactor to grow functional articular cartilage. Bovine chondrocytes are encapsulated in agarose hydrogels and subjected to physiologic loading in long-term cultures. Tissue material properties and biochemical composition are measured and compared to those of native cartilage. (no cost extension)

10. **Principal Investigator:** NIH: NIAMS 1R21 AR48791-03: *Novel Determination of chondrocyte material properties;* $75,000 yearly direct cost ($350,762 total cost), 7/1/02-6/30/05- 10% yearly effort. Description: The aim of this grant is to develop novel techniques to determine cell material properties using osmotic loading, videomicroscopy, Atomic Force Microscopy, and theoretical and computational modeling.

11. **Principal Investigator:** NIH: NIAMS 1R01AR49922-03 *Supplement:* approximate yearly direct cost:$43,000, 1/1/04-6/30/05 (total cost for entire granting period: $86,285) Description: Minority supplement for Terri-Ann Kelly (GRA) to expand the aims of the parent grant to study the inhomogeneous material and biochemical composition of rat IVD subjected to well-controlled loading regimens in an in vivo rat-tail model.

OTHER

Date of Birth:	May 18, 1968
Place of Birth:	Springfield, Massachusetts, USA
Marital Status:	Spouse: Luci Morrone, M.D., M.P.H. (Pediatrician)
Hobbies:	Tennis, Alpine Skiing, Piano/Keyboards (www.roostrock.com)